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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

MITSUBISHI TANABE PHARMA CORPORATION, *et al.*, Plaintiffs, v. SANDOZ INC., *et al.*, Defendants.	Civil Action No. 17-5319 (FLW) (DEA) (consolidated) FILED UNDER SEAL (Filed Electronically)

PLAINTIFFS' TRIAL BRIEF

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TABLE OF ABBREVIATIONS

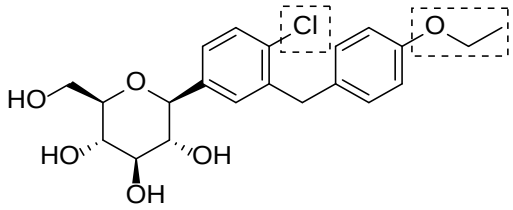
ANDA	Abbreviated New Drug Application
asserted claims	claims 12 and 20 of the ’788 patent, claim 22 of the ’219 patent, and claim 26 of the ’403 patent
BMS	Bristol Myers Squibb
DPP-4	dipeptidyl peptidase 4
Example 10	Example 10 of U.S. Patent No. 6,414,126
FDA	United States Food and Drug Administration
GLP-1	glucagon-like peptide-1
inventors	Sumihiro Nomura, Eiji Kawanishi, and Kiichiro Ueta
MTPC	Mitsubishi Tanabe Pharma Corporation or its predecessor, Tanabe Seiyaku Co., Ltd.
patents-in-suit	U.S. Patent No. 7,943,788 (“the ’788 patent”), U.S. Patent No. 8,222,219 (“the ’219 patent”), and U.S. Patent No. 8,785,403 (“the ’403 patent”)
PFOF	Plaintiffs’ Proposed Findings of Fact and Conclusions of Law, submitted concurrently herewith
Plaintiffs	MTPC, Janssen Pharmaceuticals, Inc., Janssen Pharmaceutica NV, Janssen Research and Development, LLC, and Cilag GmbH International
Plaintiffs’ Invokana® Products	Invokana®-brand canagliflozin tablets, Invokamet®-brand canagliflozin and metformin hydrochloride tablets, and extended-release Invokamet XR® tablets
POSA	person of ordinary skill in the art
PPAR	peroxisome proliferator-activated receptor
PTO	United States Patent and Trademark Office
SGLT	sodium glucose co-transporter
ZCF	Zydus’s Contested Facts, D.I. 144 Exhibit B
’117 patent	U.S. Patent No. 6,515,117
’117 patent compound	the compound disclosed in the ’117 patent
’126 patent	U.S. Patent No. 6,414,126

INTRODUCTION

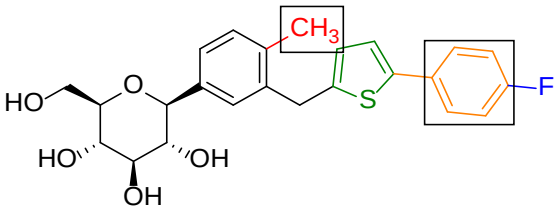
This is a Hatch-Waxman patent-infringement action involving Zydus's attempt to sell generic versions of Plaintiffs' Invokana® type 2 diabetes medication before the expiration of the patents-in-suit. The asserted claims cover the invention of the novel chemical compound known today as canagliflozin, the active ingredient in Invokana®. Some 14 generic companies have filed generic canagliflozin ANDAs, 13 of which do not challenge that canagliflozin constituted an innovation over the prior art. Zydus is alone in alleging that MTPC's discovery was obvious. In doing so, Zydus presents deeply flawed—and often self-contradictory—obviousness arguments based on unfounded assumptions and information that was not available to a POSA at the time of MTPC's invention.

Zydus's hindsight-based obviousness theory is premised on its erroneous assertion that canagliflozin was "brazenly copied (with minor modifications)" from an alleged lead compound, referred to as "the '117 patent compound."[1] Zydus will fail to prove that a POSA would have selected this compound as a lead for further development. But regardless of whether Zydus could make this threshold showing, even a cursory look at the changes it alleges a POSA would have then made to the '117 patent compound reveals there is nothing "minor" about them:

[1] D.I. 134 at 2. The only brazen copying is by Zydus, who has stipulated to infringement (D.I. 100) and is thus seeking to copy, rather than discover, a new drug compound (PFOF at ¶ 68 n.11).



The '117 patent compound



Canagliflozin

Zydus's obviousness defense would require the Court to find that Zydus has proven, by clear and convincing evidence, each of the following:

- that a POSA attempting to develop an improved antidiabetic drug would have focused on two compounds—for which no safety, efficacy, or biological data of any kind was disclosed—pertaining to a then-unproven type of diabetes treatment (*i.e.*, SGLT inhibition) and selected them as "lead compounds" for further development;
- that the POSA would have then made numerous, significant modifications to those lead compounds, including (1) changing the very structural features (in dashed-lined boxes above) that Zydus alleges would have justified their selection in the first place, (2) replacing—without knowing the effects of the changes already made—one of the two foundational "ring" structures (between the dashed-lined boxes) taught by Zydus's own references to be essential with an entirely new ring structure (in green above) that was not taught, much less preferred, by the relevant prior art, (3) proceeding to add back in—again, without knowing the effects of previous changes—the ***same ring structure just replaced*** at a different location (in orange above), and finally (4) adding yet another substituent (in blue above) under the guise of improving alleged problems introduced by its own proposed changes; and
- that the POSA would have reasonably expected these manifold changes to compounds having no data would result in a safe and effective diabetes drug.

If the Court finds that Zydus has failed to meet this heavy burden with respect to ***any one*** of the above, Zydus's defense fails. That Zydus lacks an adequate basis for all of them demonstrates the frivolous nature of its challenge.

Zydus's analysis stumbles at the first step by selecting lead compounds from

one category of potential antidiabetic treatments (*i.e.*, SGLT inhibitors) while ignoring many others available to a POSA, including categories that were more promising and already shown to be safe and effective. (*See* Section I.B.1, *infra*.) Making matters worse, Zydus selectively focuses on two SGLT compounds from one patent family, for which no prior art biological data existed, to the exclusion of many others having such data. (*See* Section I.B.2, *infra*.)

As the evidence will also show, Zydus cannot prove the remaining steps of its obviousness defense. A POSA would not have been motivated to make the numerous, complex, and contradictory changes to the structures of Zydus's lead compounds, much less at the same time given the iterative, trial-and-error nature of drug-discovery work. (*See* Section I.C, *infra*.) And even assuming, *arguendo*, that a POSA would have considered making all of these changes simultaneously, there would have been no reasonable expectation—particularly in this unpredictable field without prior art biological data—that they would have resulted in a safe and effective antidiabetic drug. (*See* Section I.D, *infra*.)

No court in a chemical compound patent case has found anything remotely close to the types and series of changes alleged by Zydus to prove an obviousness claim and, in fact, courts have rejected challenges based on far fewer and less-dramatic changes. And while unnecessary to consider given Zydus's failures of proof, objective indicia of nonobviousness further confirms the hindsight nature of

Zydus's obviousness challenge. (*See* Section I.E, *infra*.)

Zydus also attacks the statutorily authorized adjustment of the '788 patent's term by seeking to invoke the judicial doctrine of obviousness-type double patenting. But its argument conflicts with Supreme Court and Federal Circuit precedent and, as the evidence will show, is in any event prohibited by the statutory safe-harbor provision of 35 U.S.C. § 121. (*See* Section II, *infra*.)

BACKGROUND

I. Type 2 Diabetes and Its History of Treatment

Type 2 diabetes is a progressive metabolic disorder that has plagued humans for thousands of years.[2] A person suffering from diabetes is unable to generate adequate insulin to properly regulate blood glucose levels, which can cause blurred vision, weight loss, frequent urination, and other symptoms. (PFOF at ¶ 29.) If left unmanaged, diabetes can also lead to serious damage to the heart, blood vessels, eyes, kidneys, and nerves. (*Id.* at ¶ 30.)

Type 2 diabetes has generally been treated in a stepwise manner, starting with diet and exercise and then, if necessary, administering medication to help control glucose levels. (*Id.* at ¶ 39.) As of 2003, the approved drug products had various shortcomings, including administration difficulties, weight gain,

[2] PFOF at Section III.A discusses the complex and varied causes of this disorder in more detail. Type 2 diabetes accounted for approximately 90% of U.S. diabetes cases in the early 2000s, and currently affects roughly 27 million people in the U.S.

hypoglycemia, gastrointestinal effects, and/or efficacy issues. (*Id.* at Section III.B.)[3] As a result, there existed a need for an improved type 2 diabetes treatment.

In 2003, there were extensive drug-discovery efforts focused on numerous types of potential diabetes treatments.[4] For example, many researchers focused on developing compounds employing FDA-approved mechanisms of action that increased efficacy or reduced side effects compared to then-approved drugs, such as biguanides, sulfonylureas, α-glucosidase inhibitors, thiazolidinediones, and meglitinides. (*Id.* at Sections III.C, VI.C.1.a.) Numerous researchers were also working to develop compounds having mechanisms of action that, while not yet FDA-approved, were demonstrated to be viable treatment options through then-existing human clinical data, including dual-PPAR agonists, GLP-1 receptor

[3] Plaintiffs focus on the 2003 time period because, as discussed in the next section, canagliflozin was invented by October 29, 2003. Zydus, on the other hand, focuses on the July 30, 2004 application date for the '788 patent. This issue is addressed in connection with one of Zydus's pending motions *limine* (D.I. 136 & 150), and the asserted claims are nonobvious irrespective of what date is applied.

[4] As will be demonstrated at trial, drug discovery is a complex, multi-disciplinary process that typically involves: (1) selecting or identifying appropriate biological targets; (2) designing compounds to interact with those targets; (3) synthesizing and determining the new compounds' biological activities; (4) analyzing the effect(s) of structural changes on these activities; and (5) proposing and making additional modifications in an attempt to further explore biological activity. (PFOF at Section IV.B.) Because it is necessary to test each structural modification in an iterative fashion to determine if it was helpful, harmful, or neutral before determining how to proceed with respect to further modifications, this process involves significant trial-and-error experimentation. (*Id.* at ¶¶ 79-82.)

agonists, and DPP-4 inhibitors. (*Id.* at Sections III.C, VI.C.1.b.)

During this time period, some researchers were also exploring a variety of unproven treatment targets having the potential to regulate glucose levels. (*Id.* at Sections III.C, VI.C.1.c.) These categories of potential drugs included retinoid X receptor modulators, glycogen phosphorylase inhibitors, glucokinase activators, glucocorticoid receptor antagonists, and SGLT inhibitors. (*Id.*)

II. MTPC's Discovery of Invokana® and Its Transformative Impact on the Treatment of Type 2 Diabetes

MTPC was among the first pharmaceutical companies to dedicate significant resources toward researching and developing SGLT inhibitors. (*Id.* at ¶¶ 83-90.) Plaintiffs' Invokana® Products and canagliflozin, as well as other SGLT inhibitors used today, would not exist without MTPC's and the inventors' extensive efforts.[5]

As will be shown at trial, the MTPC inventors' discovery of canagliflozin involved the persistent work of more than a dozen scientists, all with experience in fields such as medicinal chemistry and pharmacology, who performed thousands of experiments from the start of the project in the early 1990s through the discovery

[5] In a misguided effort to invalidate the asserted claims, Zydus claims that MTPC did not discover canagliflozin, but allegedly "copied" and "tweaked" the work of another company. (D.I. 134 at 2.) As Plaintiffs will demonstrate at trial, this is untrue, and Zydus mischaracterizes MTPC's research efforts to make this assertion. (PFOF at Sections V.A, VI.F.) Regardless, "[t]he inventor's own path itself never leads to a conclusion of obviousness; that is hindsight." *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012).

of canagliflozin in October 2003 (and for at least a year thereafter, until canagliflozin was selected as MTPC's preferred candidate drug compound). (*Id.* at Sections V.A, VI.F.) During this decade-plus of drug-discovery work, and underscoring the unpredictable nature of this research, the inventors and other MTPC researchers tried a vast number of different approaches based on their experience, intuition, and internal (*i.e.*, non-prior art) data to identify a SGLT compound that might provide an improved diabetes treatment. (*Id.*)

The introduction of Invokana®—the first SGLT inhibitor approved in the United States—marked the start of a paradigm shift in how diabetes treatment is viewed and approached in this country. (*Id.* at Section V.B.) In addition to their ability to help manage glucose levels, the Invokana® Products currently have the broadest indication of any SGLT inhibitor for reducing cardiac complications in type 2 diabetes patients, and were the first approved for reducing the progression of kidney function reduction in such patients. (*Id.* at ¶¶ 93-110.)

III. The Patents-in-Suit

The patents-in-suit cover MTPC's discovery. Specifically, the asserted claims are directed to: (1) the novel chemical compound canagliflozin (depicted at page 2 above), the main active ingredient of the Invokana® Products; (2) a method of using canagliflozin to treat type 2 diabetes; and (3) canagliflozin in combination with metformin. (*Id.* at Section II.) The key question with respect to the patents-

in-suit is whether Zydus has proven by clear and convincing evidence, and without hindsight, that canagliflozin would have been obvious to a POSA.

ARGUMENT

I. Zydus Will Not Prove Obviousness of the Asserted Claims by Clear and Convincing Evidence

A. The Applicable Legal Standard

The patents-in-suit are presumed to be valid and, as such, Zydus bears the burden of proving by "clear and convincing evidence" that the asserted claims would have been obvious to a POSA[6] at the time of the invention under 35 U.S.C. § 103. *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 95 (2011). In this case, Zydus "bears a difficult burden" because its prior art references were already considered by the PTO in allowing the asserted claims. *See, e.g.*, *Cadence Pharm. Inc. v. Exela Pharmsci Inc.*, 780 F.3d 1364, 1375 (Fed. Cir. 2015).

Obviousness is determined by evaluating the well-known "*Graham* factors": (1) the level of ordinary skill in the pertinent art; (2) the scope and content of the prior art; (3) the differences between the claimed invention and the prior art; and (4) any "objective indicia" of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)). This analysis includes considering whether a POSA "would

[6] Zydus does not dispute that a POSA would have had a graduate degree in medicinal chemistry, pharmacology, and/or related field, with experience in developing pharmaceutical compositions and an awareness of the antidiabetic drug field. (*See* ZCF at 3.)

have been motivated to combine the teachings of the prior art to achieve the claimed invention, and . . . had a reasonable expectation of success in doing so." *InSite Vision, Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859-61 (Fed. Cir. 2015).

An important aspect of the "motivation" analysis is identifying the "problem facing those skilled in the art at the time the invention was made," which "is not [limited to] the specific problem solved by the invention." *Id.* at 859-60 ("Defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness."). Instead, "[w]hether a [POSA] would narrow the research focus to lead to the invention depends on the facts." *Id.* at 860. The undisputed record evidence shows that the problem facing a POSA in this case was developing an improved type 2 diabetes treatment. (PFOF at ¶ 123.)

When, as here, a defendant alleges that "a new chemical compound would have been *prima facie* obvious over particular prior art compounds," it must be established that a POSA "would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts." *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012). A lead compound is a "compound in the prior art that would be most promising to modify in order to improve upon its . . . activity and obtain a compound with better activity." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007). In determining whether a POSA would have selected a

compound as a lead, "the analysis is guided by evidence of the compound's pertinent properties." *Otsuka*, 678 F.3d at 1292 (referring to "activity and potency, adverse effects such as toxicity, and other relevant characteristics in evidence"); *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) ("Potent and promising activity . . . trumps mere structural relationships.").

Assuming this requirement is satisfied, a defendant must also establish that "the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention," *Takeda*, 492 F.3d at 1356, with "a reasonable expectation of success," *Otsuka*, 678 F.3d at 1292; *see also Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) (defining success as "finding a compound that had high activity, few side effects, and lacked toxicity," as opposed to "baseline" activity).

As explained below, Zydus cannot come close to proving any of these requirements by clear and convincing evidence, let alone all of them.

B. Without Using Improper Hindsight, Zydus Will Not Perform a Reasoned Lead Compound Analysis

Zydus contends that two prior art SGLT compounds, the '117 patent compound—which Zydus ***did not identify as a potential lead compound*** when initially creating its obviousness defense (PFOF at ¶ 170 n.26)—and "Example 10" from the '126 patent, would have been selected by a POSA as lead compounds for further development. (ZCF at 86-91, 131-34.) Zydus will not establish by clear

and convincing evidence that a POSA would have chosen these compounds as leads because: (1) Zydus uses hindsight to focus on SGLT inhibitors to the exclusion of other more promising antidiabetic compounds; and (2) even if SGLT inhibitors were the sole focus, Zydus selects two compounds (from the same patent family) that had no known biological data while ignoring numerous compounds having safety and efficacy data, including one that was known to be in clinical development.

1. Zydus's Myopic Lead Compound Analysis Ignores the Problem Facing a POSA

Zydus's obviousness analysis is fundamentally flawed from the outset. The undisputed evidence at trial will show that the problem facing a POSA was developing an improved ***antidiabetic*** treatment. (PFOF at ¶ 123.) Yet, using hindsight, Zydus focuses exclusively on one narrow aspect of the ***SGLT*** prior art for its alleged lead compounds. (*See* Section I.B.2, *infra*.) This is improper. *See InSite*, 783 F.3d at 859-61 ("[T]he problem faced by one skilled in the art was broader than merely seeking to use [a specific drug] to treat [a specific disease].").

As explained in the Background Section above, many of the top pharmaceutical companies around the world in 2003 were attempting to create safe and effective type 2 diabetes treatments through a variety of methods and pathways, including dozens of promising clinical candidates having FDA-approved

mechanisms of action and/or robust efficacy data in humans.[7] Even Zydus's own medicinal chemistry expert, Dr. Thomas Bannister, was researching GLP-1 receptor agonists, ***not*** SGLT inhibitors, during the relevant time period. And because time and resources would have been finite, a POSA would have focused on a limited number of lead compounds taken from these different treatment approaches for further development. (PFOF at ¶ 77.)

Zydus eschews all of these potential lead compounds in favor of SGLT compounds, even though there was ***no*** prior art evidence that such compounds were efficacious in humans.[8] As such, Zydus's lead compound analysis cannot, without hindsight, justify selecting only such compounds "over other compounds ***in the prior art***," *Daiichi*, 619 F.3d at 1354,[9] which indisputably included many promising non-SGLT antidiabetic compounds. (PFOF at Sections III.C, VI.C.1.)

[7] Examples of such compounds include CKD-711 (α-glucosidase inhibitor), "MCC-555" (thiazolidinedione), "KAD1229" (meglitinide), "BMS 298585" and "AZ-242" (dual PPAR agonists), "NN-2211" and "AC-2993" (GLP-1 receptor agonists), as well as "NVP-LAF-237" (DPP-4 inhibitor). (PFOF at Sections III.C, VI.C.1.a-b.)

[8] Consistent with this fact, numerous scientific publications summarizing potential diabetes treatments in development in the relevant time period did not even mention SGLT inhibitors (*id.* at ¶ 337), which were the subject of skepticism in the field (*id.* at Sections VI.C.1.d, IX.B). This real-world evidence further illustrates the misguided nature of Zydus's hindsight focus on only SGLT compounds.

[9] Unless otherwise indicated, all emphases have been added and citations omitted.

2. Zydus Will Not Establish That a POSA Would Have Selected Its Leads over Other Prior Art SGLT Compounds

Even assuming, *arguendo*, that a POSA would have focused on only SGLT inhibitors, Zydus's lead compound analysis is still deficient because it cherry-picks two SGLT compounds—from a single BMS patent family directed to what Zydus refers to as "C-glucosides" (PFOF at ¶ 154)—for which no biological data was disclosed, while ignoring SGLTs from other companies having such data.

(a) Zydus Fails to Justify Its Focus on the '117 Patent Compound

Zydus's first alleged lead is the '117 patent compound.[10] (ZCF at 86.) When Zydus first challenged the patents-in-suit as obvious in its notice letters, it did not identify the '117 patent compound as an alleged lead. (PFOF at ¶ 170 n.26.) Nor did the PTO when examining the patents-in-suit. (*Id.* at ¶ 176.) If Zydus could not identify this compound as a lead when it served its notice letters in 2017, it certainly would not have been obvious to a POSA in 2003.

Zydus contends that a POSA would have inferred that the '117 patent compound had promising properties—despite not disclosing any biological data associated with that compound—merely because it was the only compound identified in that particular patent. (ZCF at 88.) But this patent was just one of

[10] Zydus refers to this compound as "dapagliflozin," but that name does not appear in the prior art. Accordingly, Plaintiffs refer to it as "the '117 patent compound."

many filed by BMS. And this BMS patent does not assert, much less provide support for concluding, that the compound was more promising than many other prior art SGLT compounds (let alone the numerous other promising non-SGLT compounds discussed above) being studied by BMS and other companies, including those with available safety and efficacy data. (PFOF at Section VI.C.3.)[11]

For example, in connection with its motivation arguments, Zydus relies on at least 25 SGLT compounds (which it refers to as "O-glucosides") with disclosed activity data, including one, "T-1095," that was known to be in clinical trials. (*Id.* at ¶¶ 154, 157.) Zydus's self-contradictory use of certain references disclosing more promising compounds for its hindsight-based motivation arguments, while ignoring them in making hindsight-based lead compound arguments, warrants rejecting its analysis. *See, e.g.*, *Daiichi*, 619 F.3d at 1353-54 (rejecting proposed leads, despite being described as having "remarkable and unexpected potency" based on *in vivo* data, because a POSA would not have selected them over a

[11] Zydus may cite the "WO '209" application as part of its arguments for selecting the '117 patent compound. But this document is not prior art (PFOF at ¶ 512 n.111) and, even if it were, it still would not support Zydus's arguments. WO '209 is merely an application directed to the process of making compounds that also disclosed no biological data, and thus would not have motivated a POSA to select the '117 patent compound (or any other compound) as a lead. (*Id*. at ¶¶ 173-74.) This is consistent with the PTO—just like Zydus in 2017—not identifying that compound as a potential lead despite considering WO '209. (*Id*. at ¶ 176.)

handful of "more thoroughly studied" compounds having more advanced data); *Merck Sharp & Dohme Corp. v. Sandoz Inc.*, No. 12-3289, 2015 WL 5089543, at *41-43 (D.N.J. Aug. 27, 2015) ("As in *Daiichi*, the lack of pharmaceutical data available on the [proposed lead] compound in question renders [the claimed invention] non-obvious in light of the available data on other compounds.").

Zydus broadly dismisses these O-glucosides by asserting they would have been perceived as suffering from "stability issues" preventing SGLT inhibition after oral administration. (PFOF at VI.C.2.) But Zydus's own references put the lie to that assertion,[12] and the prior art evidence at trial will show that dozens of O-glucosides were known to inhibit SGLT after oral administration. (*Id.* at ¶ 157.)

In any event, Zydus's argument is readily dispelled by the fact that BMS—whose compounds are Zydus's exclusive focus—***continued pursuit of O-glucosides even after applying for the '117 patent***. (*Id.* at ¶ 167.) This further demonstrates the misguided nature of Zydus's hindsight focus on C-glucosides.

(b) Zydus Fails to Justify Its Focus on Example 10

Zydus's second alleged lead compound ("Example 10," from an earlier BMS patent, the '126 patent) fares no better. Zydus alleges that a POSA would have selected Example 10 because it is among the "most preferred" compounds of the

[12] Even Zydus's 2004 and 2005 (non-prior art) references discuss O-glucosides without noting any stability-related issues (*id.* at ¶ 168), and a 2009 reference states that, before 2005, patents "predominantly featured novel O-glucosides" (*id.*).

'126 patent and appears in claim 10 of the '126 patent. (ZCF at 131.) Many billions of compounds, however, fall within this same "most preferred" grouping, and Example 10 is only one of 80 examples in that patent, many of which also fall within this grouping. (PFOF at ¶ 178.) Further, 14 other compounds are listed in claim 10, and more than 35 additional compounds are specifically identified in other claims. (*Id.*) Zydus plainly uses hindsight to choose Example 10: It cannot prove by clear and convincing evidence that a POSA would have selected Example 10 over these other BMS compounds, much less the numerous compounds being developed for which biological data was disclosed. *See*, *e.g.*, *Daiichi*, 619 F.3d at 1353-54.[13]

Given the limited number of lead compounds on which a POSA could reasonably have focused in attempting to develop an improved antidiabetic drug, Zydus cannot establish by clear and convincing evidence and without hindsight that either the '117 patent compound or Example 10 would have been chosen as leads for further development.

[13] Zydus has attempted to justify Example 10 based on the "WO '066" application, which discusses certain experiments using Example 10 and other BMS compounds. These Example 10 experiments, however, were not successful. (PFOF at ¶ 181.) Zydus fails to explain how such failed experiments could have prompted a POSA to select Example 10 over other prior art compounds, including those discussed in WO '066. In fact, despite considering the '126 patent and WO '066, the PTO never identified Example 10 as a potential lead. (*Id.* at ¶ 182.)

C. Zydus Will Not Prove That a POSA Would Have Been Motivated to Make the Necessary Specific Molecular Modifications to Its Alleged Lead Compounds

Even assuming a POSA would have selected Zydus's lead compounds, its argument further requires the POSA to have been motivated to make four (with respect to the '117 patent compound) or three (with respect to Example 10) significant structural modifications—all at the same time and without changing any other aspects of the alleged leads—as summarized below:

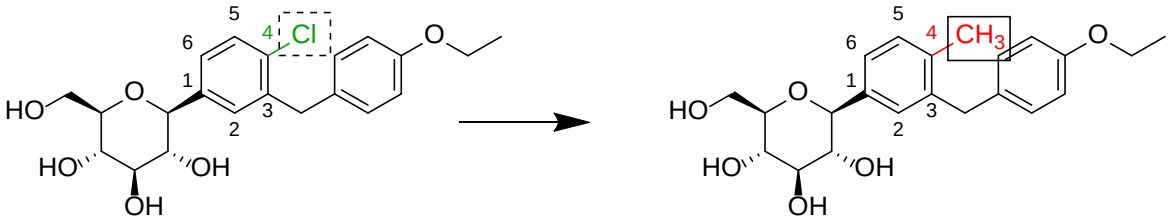
- Change the "4-chloro" of the '117 patent compound to a "4-methyl" (while not making any modification to Example 10 at the same location);
- Change only the distal "phenyl" ring of both the '117 patent compound and Example 10 to a "thiophene" ring in a specific orientation;
- Change the "4-ethoxy" of the '117 patent compound and the "4-thiomethyl" of Example 10 to a new phenyl ring at a particular location; and
- Change one hydrogen to a single fluorine atom at a particular location of the new phenyl ring.

As explained below and will be demonstrated at trial, Zydus's proposed changes are inconsistent and lack prior art support. Even worse, they are ***contradicted by the very BMS patents*** on which Zydus alleges a POSA would have focused.

1. Zydus Will Not Prove That a POSA Would Have Been Motivated to Change the 4-Chloro Group of the '117 Patent Compound

Zydus asserts that a POSA would have changed the "4-chloro" group of the '117 patent compound (in green) to a "4-methyl" group (in red):

Zydus's Proposed 4-Chloro Change



The '117 patent compound

This structural modification, however, contradicts Zydus's reason for selecting this compound as a lead in the first place. (PFOF at ¶¶ 194-95.) Namely, the 4-chloro was one of two features that, under Zydus's flawed theory, allegedly justified selecting the '117 patent compound over other prior art C-glucosides. (*Id.*) But a POSA would not have selected a lead "only to disregard one of their distinguishing characteristics" when making modifications. *Daiichi*, 619 F.3d at 1356.[14]

Zydus contends that a POSA would have allegedly made this change "to design around the prior art" and "circumvent a conflicting patent situation with potential competitors." (ZCF at 107-08.)[15] Even putting aside that a POSA would not have been focused on designing around BMS's patents (PFOF at ¶¶ 202, 208),

[14] *See also Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1358-59 (Fed. Cir. 2008) ("The record, however, shows no discernible reason for a skilled artisan to begin with [a lead compound] only to drop the very feature . . . that gave this advantageous property."). As explained in Section I.C.3, Zydus also proposes changing the only other distinguishing feature (among other significant changes).

[15] To the extent this was the POSA's goal, it could have been achieved by making any number of modifications, including many that Zydus ignores. (PFOF at ¶ 202 n.42.) And, as explained below, that Zydus's analysis requires a POSA to continue making modifications after "designing around"—purportedly simply to "maintain activity"—further exposes the hindsight nature of its analysis.

Zydus's proposed 4-methyl substituent would ***not*** "design around" those patents, as it would fall squarely within the scope of the '126 patent (*id.* at ¶¶ 195, 290).

Recognizing this, Zydus also argues that a POSA would have allegedly understood 4-chloro and 4-methyl to be "roughly equally valid options" according to BMS's '126 patent and other references. (ZCF at 108-09.)[16] That assertion lacks support, and a POSA would not have pursued "roughly equally valid options" when faced with the problem of developing an ***improved*** type 2 diabetes treatment. *InSite*, 783 F.3d at 859-61.[17] In short, Zydus will not prove that a POSA would have pursued an "equally valid option" from the same patent that the POSA, according to Zydus, is purportedly attempting to design around.

Zydus's "roughly equally valid" approach, if accepted, would also apply to countless other potential prior art modifications, none of which would have resulted in the claimed inventions. (PFOF at ¶ 197.) This logical problem with its argument demonstrates that Zydus will fall woefully short of proving by clear and

[16] Zydus does not assert that a POSA would have explored any allegedly "equally valid options" in connection with its other lead compound, Example 10, including changing the 4-methyl of that compound to a 4-chloro. (PFOF at ¶ 196 n.39.) This is yet another inconsistency that demonstrates Zydus's approach of cherry-picking disparate features of the prior art without adequate justification to arrive, with hindsight, at the compound now known as canagliflozin.

[17] Zydus's own cited references also disclose that a methyl group could potentially suffer from metabolic instability. (*Id.* at ¶¶ 198, 296.) By contrast, Zydus alleges that a POSA would have made other changes to avoid such potential instability concerns (ZCF at 120-22), which is yet another inconsistency in its analysis.

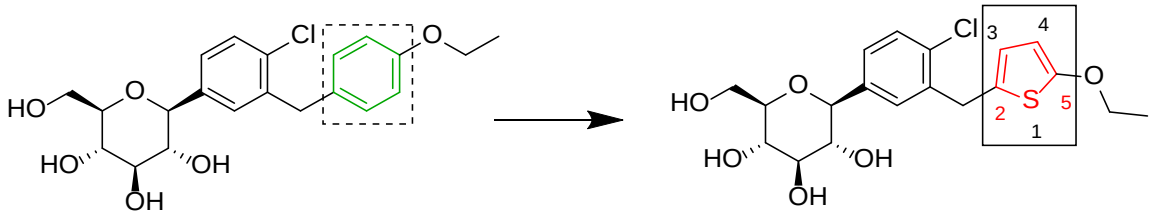
convincing evidence the "specific molecular modifications necessary to achieve the claimed invention." *See, e.g.*, *Takeda.*, 492 F.3d at 1360 (affirming no motivation when a POSA would, *inter alia*, "look at a host of substituents, such as chlorides, halides and others, not just methyls" for potential modifications); *Pfizer Inc. v. Teva Pharm. USA, Inc.*, 555 Fed. App'x 961, 971 (Fed. Cir. 2014) (non-precedential) (affirming no motivation when prior art references relied upon by defendant disclosed "millions of potential compounds" without "any teaching particularly identifying" the alleged modification) (citing *Takeda*).[18]

2. Zydus Will Not Prove That a POSA Would Have Been Motivated to Change the Distal Phenyl of Its Lead Compounds

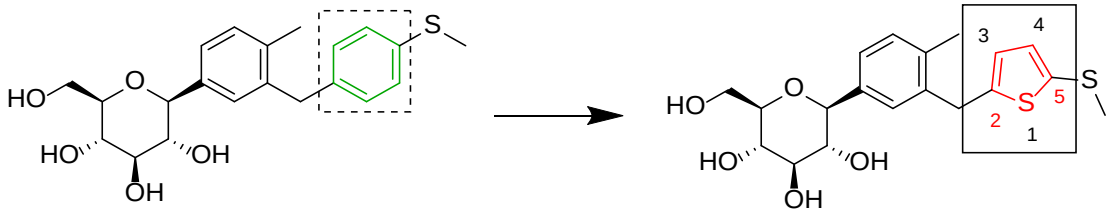
Zydus not only abandons the structural features that allegedly distinguish its proposed leads from the '126 and '117 patents, it seeks to modify the ring structure required in ***every one*** ***of the billions of compounds in those patents***. Specifically, Zydus asserts that a POSA would have eliminated the distal phenyl ring of its lead compounds (in green) and used a thiophene ring in a "2, 5 orientation" (in red):

[18] Zydus frequently discusses what a POSA could have allegedly done "without undue experimentation." (*E.g.*, ZCF at 103, 112, 122, 123-25 (asserting analysis is "[n]ot [h]indsight" because "optimization would have been accomplished without undue experimentation").) Aside from being inaccurate, these hindsight assertions are irrelevant. *See, e.g.*, *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1310 (Fed. Cir. 2015) (contrasting obviousness analysis with whether a POSA could "make and use the claimed invention without undue experimentation").

Zydus's Proposed Distal Phenyl Ring Change



The '117 patent compound



Example 10 of the '126 patent

Zydus contends that a POSA would have made these modifications in an effort to "maintain efficacy." (ZCF at 97.)[19] But the prior art SGLT literature does not provide any support that such a phenyl-to-thiophene modification would have "maintain[ed] efficacy."[20] In fact, Zydus does not reference ***a single*** thiophene-containing prior art C-glucoside compound. As such, and other than proceeding blatantly with hindsight, Zydus has to resort to misapplying a highly generalized

[19] Merely maintaining efficacy would not have motivated a POSA seeking to develop an improved antidiabetic (PFOF at ¶¶ 248, 268), and there was no efficacy data for either alleged lead compound to serve as a reference to "maintain."

[20] Zydus does not identify any thiophene-containing SGLT compounds that would have guided a POSA to change a phenyl ring to a thiophene ring (much less in the orientation present in canagliflozin) over other potential modifications, let alone prove that such a change would "maintain activity." (PFOF at Section VI.D.2.)

medicinal chemistry concept called "bioisosterism."[21] (ZCF at 101-07.)

As courts have repeatedly recognized, bioisosterism falls far short of providing the requisite motivation to make a specific molecular modification. *See, e.g.*, *Eli Lilly*, 689 F.3d at 1378 (Fed. Cir. 2012) (finding "bioisosterism" would not have motivated thiophene to phenyl change); *Yamanouchi*, 231 F.3d at 1344-45 (rejecting "bioisosteric substitution" theory); *Mylan Pharm. Inc. v. Research Corp. Techs., Inc.*, 914 F.3d 1366, 1376 (Fed. Cir. 2019) (same). This is because "a POSA would not have been able to predict the effect of a bioisosteric substitution," which "can change the way a molecule interacts with biological receptors" and "drastically impact drug performance," *UCB, Inc. v. Accord Healthcare, Inc.*, 201 F. Supp. 3d 491, 543 (D. Del. 2016), *aff'd*, 890 F.3d 1313 (Fed. Cir. 2018),[22] as confirmed by Zydus's own references (PFOF at ¶¶ 206-07, 297-300).

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[21] Bioisosterism is generally discussed in connection with series of compounds already studied. As such, "[b]ioisosterism refers to a process that involves replacing one atom or functional group in a molecule with another of similar chemical, physical, or electronic properties in ***hopes*** that the substitution will result in similar or enhanced activity." *Eli Lilly & Co. v. Teva Parenteral Medicines, Inc.*, 689 F.3d 1368, 1377 n.6 (Fed. Cir. 2012); *see also* PFOF at ¶¶ 205-08.

[22] To arrive at these conclusions, the *UCB* court rejected "bioisosterism" opinions from Dr. Clayton Heathcock that are virtually identical to the ones offered by Zydus in this case. This is not surprising, as Dr. Heathcock was Zydus's original medicinal chemistry expert. (PFOF at ¶ 137 n.18.) Zydus subsequently replaced Dr. Heathcock with Dr. Bannister, but his "bioisosterism" opinions suffer from the same deficiencies rejected in *UCB*. *See also Mylan Pharm.*, 914 F.3d at 1376 (affirming rejection of Dr. Heathcock's bioisosterism opinions).

Even assuming bioisosterism was utilized as Zydus alleges, a POSA would have had to consider many "bioisosteric replacements," with no relevant biological data that would justify selecting one over any other. (*Id.* at Section VI.D.2.b.)[23] This provides an independent basis for rejecting this alleged motivation. *E.g.*, *Eli Lilly*, 689 F. 3d at 1378 (finding no motivation due to "many opportunities for modification").[24] And even assuming a POSA would have identified thiophene as a potential "bioisosteric replacement" for phenyl, the SGLT prior art suggested this substitution would adversely affect activity. (PFOF at ¶¶ 210-14.) In short, reliance on "bioisosterism" simply reflects that a patent challenger like Zydus is unable to find adequate prior art support for a proposed modification.

Yet, the situation is far worse for Zydus; the prior art as a whole teaches that both phenyl rings are required for the C-glucosides on which it focuses. Specifically, the BMS '117 and '126 patents do not permit a thiophene—or ***any***

[23] Zydus asserts that thiophene is "the most common ring bioisostere for phenyl." (ZCF at 101.) As the evidence at trial will show, however, this argument is neither supported by Zydus's own references nor consistent with how a POSA would have viewed bioisosteric modifications. (PFOF at ¶¶ 219-22.)

[24] Zydus makes the equally baseless assertion that a phenyl-to-thiophene substitution was somehow "obvious to try." (ZCF at 103.) Such a theory applies only when the prior art options are "finite," "small," or "easily traversed." *In re Cyclobenzaprine*, 676 F.3d 1063, 1072-73 (Fed. Cir. 2012) ("[W]here the prior art, at best, '[gives] only general guidance as to the particular form of the claimed invention or how to achieve it, relying on an 'obvious-to-try' theory to support an obviousness finding is 'impermissible.'"); *see also Takeda*, 492 F.3d at 1359 (rejecting "obvious to try" rationale in chemical compound case).

other ring besides phenyl—in the many billions of disclosed C-glucoside structures. (*Id.* at ¶ 215.) By contrast, BMS's O-glucoside patent applications—whose relevant disclosures for their respective compounds mirror those in the '117 and '126 patents—allow numerous variations in these ring locations. (*Id.* at ¶ 216 n.46.) This difference in permissible ring structures would be understood by a POSA to be purposeful, and thus teaches away. *See, e.g.*, *Daiichi*, 619 F.3d at 1354-55 (affirming teaching away from a specific substitution where "the vast majority, thirty-six out of forty-two compounds," did not possess that substitution).

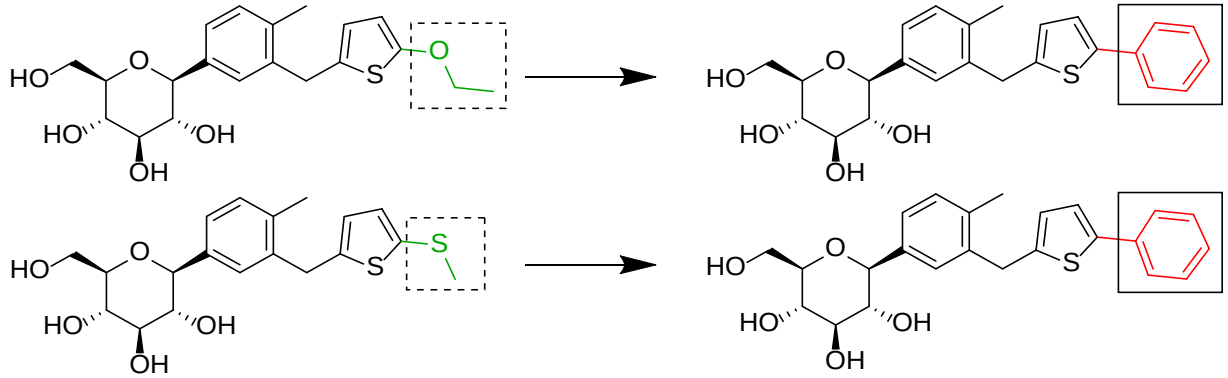
3. Zydus Will Not Prove That a POSA Would Have Been Motivated to Reinsert a Phenyl Ring into Its Lead Compounds

Incredibly, Zydus's *third* proposed modification—which it contends a POSA would have made without knowing whether the alleged modifications made so far were helpful[25]—is to ***add back in the phenyl ring it just argued a POSA would have been motivated to remove***.[26]

[25] Zydus has not argued that a POSA could have made this proposed modification before the two previous modifications discussed above. *See, e.g.*, *Yamanouchi*, 231 F.3d at 1345 (finding no motivation to modify where "the prior art offer[ed] no suggestion to pursue the particular order of manipulating parts of the compounds" required by the defendant's "very specific series of steps"). This provides yet another, independent basis upon which to reject Zydus's obviousness theories.

[26] Even worse, as shown in the illustration on page 2, this resurrected phenyl ring (in orange) replaces the only other feature serving as the purported basis for distinguishing Zydus's alleged lead compounds over other prior art compounds. As discussed in Section I.C.1 above, this is contrary to Federal Circuit precedent.

Zydus's Proposed Reintroduction of a Phenyl Ring



This self-contradiction strains credulity, to say the least, and further confirms the frivolity of Zydus's obviousness defense.

Zydus once again contends that this third modification would have been made "to improve or at least maintain activity." (ZCF at 110.) Zydus does not even attempt prove that a POSA would make yet another change having just made two modifications that Zydus alleges would have been expected to be successful.[27]

Regardless, Zydus fails to point to a single prior art SGLT compound having a first phenyl ring, a second thiophene ring, and a third phenyl ring. As such, it must cite a '126 patent example falling outside the "most preferred" group[28] (ZCF

[27] As explained in the next section, Zydus goes on to allege that this proposed modification would have created a "stability" issue that requires yet another substitution. A POSA, however, would not act in such an irrational fashion. *See, e.g., Yamanouchi Pharm. Co. v. Danbury Pharmacal*, 21 F. Supp. 2d 366, 373 n.13 (S.D.N.Y. 1998) (explaining that a POSA "thinks along the line of conventional wisdom" and does not "innovate," including through "expensive, systematic research or by extraordinary insights"), *aff'd*, 231 F.3d 1339 (Fed. Cir. 2000).

[28] This is in stark contrast to Zydus's reliance on this same most preferred group teaching with respect to other proposed changes. (*See* Section I.C.1, *supra*.)

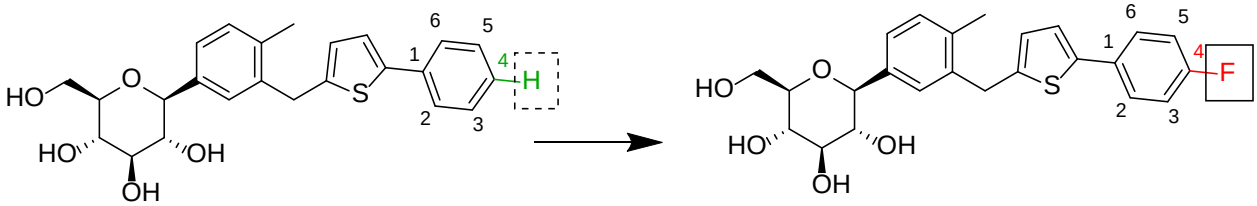
at 110)—which Zydus does not consider as a potential lead—that is one of billions of compounds disclosed in this document. (PFOF at ¶ 257.) Even ignoring this glaring inconsistency between Zydus's motivation theories, according to Zydus, a POSA would have needed to consider billions of other options, with no biological data on which to rely to justify selecting one over any other. (*Id.*)

Zydus again attempts to rely on "bioisosterism" to justify its selection (ZCF at 111), but not even its own references support this proposed modification. (*Id.* at ¶¶ 259-62, 274-75.) As such, this position is also "utterly frivolous." *Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc.*, 549 F.3d 1381, 1389 (Fed. Cir. 2008) (affirming exceptional case based upon "bioisostere" argument).

4. Zydus Will Not Prove That a POSA Would Have Been Motivated to Add a 4-Fluoro to Only the New Distal Phenyl of Its Lead Compounds

Even after all of the unsupported modifications discussed above, Zydus's obviousness analysis requires a POSA—again, without any changes made thus far having been shown to be beneficial—to have replaced the "4-hydrogen" (in green) of the alleged new phenyl ring with a "4-fluoro" (in red):

Zydus's Proposed 4-Fluoro Addition



Zydus asserts that a POSA would have been motivated to make this modification based on an alleged concern that the novel compound containing the new third phenyl ring (resulting from its third proposed modification) would be unstable. (ZCF at 120-23.) As an initial matter, if anything, this provides a reason for a POSA to have not made the modifications raising this issue in the first place. (PFOF at ¶¶ 282-83.) Regardless, a POSA would not have known that the novel compound suffered from any such stability problem (*id.* at ¶ 282), and a "fluorination strategy" was known to raise other potential issues (*id.* at ¶ 284). Given such complexities, a POSA would not have turned to a fluorination approach to "solve an undefined problem." *See, e.g.*, *Amerigen Pharm. Ltd. v. UCB Pharma GmbH*, 913 F.3d 1076, 1087 (Fed. Cir. 2019) (affirming a lack of motivation to solve a bioavailability problem that was unknown in the prior art); *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1356-57 (Fed. Cir. 2013) (finding that a modification would not have been obvious to try because the POSA "would not have recognized the problem"). In fact, the '126 patent example upon which Zydus relies to reinsert the phenyl ring does not contain such a fluorine, and it is not a "most preferred" substitution at this location.[29] (PFOF at ¶¶ 256-57, 286.)

[29] In contrast, the '126 patent discloses that making this same fluoro substitution on the first phenyl ring is "most preferred," which Zydus ignores in connection with its motivation analysis. (PFOF at ¶ 197.) This provides yet another basis to reject Zydus's inconsistent obviousness defense.

Even assuming a POSA would have considered a fluorination strategy to solve Zydus's manufactured "stability issue," Zydus fails to establish that any of its cited references would have motivated a POSA to try only a single fluoro substitution at one position on the new phenyl ring, as opposed to many other locations on the compound. (PFOF at ¶ 287.) That Zydus's analysis requires a POSA to have searched for the optimal location of a fluorine atom in a previously unknown compound only further increases the number of possibilities a POSA would have needed to consider in connection with every other proposed modification—which was already into the billions, as explained above.

As will be demonstrated at trial, Zydus's motivation arguments contradict one another between alleged modifications, lack support in its own references, and ignore countless other potential modifications that a POSA would have needed to consider according to Zydus's analysis. They should be rejected accordingly.

D. Zydus Will Not Prove That a POSA Would Have Had a Reasonable Expectation of Success

According to Zydus's own requirements (ZCF at 27, 129), a POSA would have sought an improved type 2 diabetes treatment with properties similar to or better than those possessed by Zydus's lead compounds, such as: (1) *in vitro* SGLT2 potency; (2) high SGLT2 selectivity, including over SGLT1[30] activity;

[30] "SGLT1" and "SGLT2" are the SGLTs present in the kidney. (PFOF at ¶ 60.)

(3) *in vivo* efficacy after oral administration; and (4) low kidney toxicity. *See, e.g.*, *Yamanouchi* 231 F.3d at 1345 (defining "success" as "finding a compound that had high activity, few side effects, and lacked toxicity"). Zydus cannot prove that even its own selected lead compounds possessed all of these attributes given the absence of any prior art biological data associated with them. (PFOF at ¶ 295.) Even if Zydus could demonstrate this, however, in light of the complexities of antidiabetic drug design and unpredictability of medicinal chemistry[31]—where even arguably "small" changes can significantly affect the characteristics and properties of a compound[32]—Zydus cannot prove that a POSA would have reasonably expected that the compound resulting from its multiple, significant proposed modifications would have similar, much less improved, properties. (PFOF at ¶ 298.)

This uncertainty is only compounded by the fact that many of Zydus's proposed modifications are not based on preferred groups, or even taught by its cited references. (*Id*. at ¶¶ 291, 295.) For example, Zydus fails to point to prior art data suggesting that a POSA should pursue a SGLT compound having a first phenyl ring, second thiophene ring, and third phenyl ring, let alone that it would be

[31] Zydus recognizes that drug discovery is a "highly iterative process" that typically involves "incremental" testing of one "small change in structure" at a time to determine if it had "[n]egative" or "positive" effects on various drug properties before potentially making further modifications. (ZCF at 10-11.)

[32] "[T]o the extent an art is unpredictable, as the chemical arts often are[,] potential solutions are less likely to be genuinely predictable." *Eisai*, 533 F.3d at 1359.

selective for SGLT2 over SLGT1, efficacious after oral administration, and have low kidney toxicity. (ZCF at 129-30.) Particularly in light of the numerous examples of unpredictability in the SGLT field, including with respect to the types of substitutions Zydus alleges here (PFOF at ¶¶ 297-99), specific prior art disclosures or data are necessary to support a reasonable expectation of success. *See, e.g.*, *Takeda*, 492 F.3d at 1360 (affirming no reasonable expectation of success where data did not show that "a methyl group . . . would reduce or eliminate its toxicity"); *Merck*, 2015 WL 5089543, at *29 (finding no reasonable expectation of success "without the benefit of any biological and pharmacokinetic data").

Tacitly conceding the lack of such support in the prior art, Zydus resorts to relying on the confidential internal data of the canagliflozin inventors. (ZCF at 123-28.) This runs afoul of Federal Circuit and statutory law. *See, e.g.*, *Otsuka*, 678 F.3d at 1296 ("The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight."); *In re Kratz*, 592 F.2d 1169, 1175 (C.C.P.A. 1979) ("The last sentence of 35 U.S.C. § 103, with great clarity, excludes such methodology."). Moreover, as will be demonstrated at trial, Zydus mischaracterizes MTPC's internal work, which, if anything, further reflects the deficiencies of its defense. (PFOF at Section VI.F.)

E. Objective Indicia of Nonobviousness Confirm That Zydus Will Not Establish Obviousness of the Asserted Claims by Clear and Convincing Evidence

Zydus will fail to prove the selection of a lead compound, motivation to modify, and reasonable expectation of success, which alone is sufficient to reject its defense. *See, e.g.*, *Yamanouchi*, 231 F.3d at 1345. Nonetheless, evidence of objective indicia confirms that Zydus's obviousness allegations are infected with hindsight and disconnected from real-world facts,[33] including:

- **Unexpected Properties:** Canagliflozin has superior glycemic control compared to the '117 patent compound, as evidenced by clinical trial analyses and their FDA-approved labels. (PFOF at Section IX.A.)[34]
- **Skepticism:** Skepticism surrounded the development of SGLT inhibitors as a potential diabetes treatment, which resulted in many top pharmaceutical companies directing resources to other approaches. (*Id.* at Section IX.B.)
- **Failure of Others:** Certain pharmaceutical companies tried, but failed, to develop a SGLT inhibitor drug product. (*Id.* at Section IX.C.)
- **Long-Felt Need:** As the first FDA-approved SGLT2 inhibitor, the Invokana® Products satisfied a long-left and unmet need for an improved type 2 diabetes treatment in the United States. (*Id.* at Section IX.D.)
- **Industry Praise:** Canagliflozin has also received significant industry recognition and praise from the medical community and health care professionals, including within the past year. (*Id.* at Section IX.E.)

[33] Zydus has the burden of establishing obviousness, which includes consideration of objective indicia. *See, e.g.*, *Cyclobenzaprine*, 676 F.3d at 1079 n.5. "These objective considerations can protect against the prejudice of hindsight bias, which often overlooks that 'the genius of invention is often a combination of known elements which in hindsight seems preordained.'" *Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc.*, 711 F.3d 1348, 1368 (Fed. Cir. 2013).

[34] The required nexus between the advantageous properties of the Invokana® Products, which flow from the active ingredient canagliflozin (PFOF at ¶¶ 321-22), and the asserted claims covering that ingredient is presumed. *See, e.g.*, *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329-30 (Fed. Cir. 2016).

- **Copying and Acquiescence:** 14 companies are seeking to make generic versions of the Invokana® Products, but only one, Zydus, is alleging that the asserted claims would have been obvious. (*Id.* at Section IX.F.)
- **Commercial Success:** The Invokana® Products have been commercially successful, which would have motivated competitors to develop them earlier if canagliflozin was in fact obvious. (*Id.* at Section IX.G.)

For the foregoing reasons, as well as the facts that will be proven at trial, the Court should hold that Zydus has not met its burden of proving by clear and convincing evidence that the asserted claims would have been obvious to a POSA at the time of the invention.

II. Zydus Will Not Prove Obviousness-Type Double Patenting by Clear and Convincing Evidence

Zydus argues that claims 12 and 20 of the '788 patent are invalid for obviousness-type double patenting over claim 22 of the '219 patent because the '788 patent's patent term adjustment ("PTA") extends beyond the expiration date of the '219 patent. (ZCF at 203-04.) As explained below, Zydus's defense is based upon a judicial doctrine, which cannot override a statutorily authorized term extension, such as a PTA. (*See* Section II.B, *infra*.) In any event, Zydus is barred from making this argument by the statutory safe harbor provision set forth in 35 U.S.C. § 121. (*See* Section II.C, *infra*.)

A. Background Relevant to the Parties' Double Patenting Dispute: The PTO Granted a Patent Term Adjustment for the '788 Patent

The '788 and '219 patents both claim priority to the same July 30, 2004 patent application, but their respective claims had to be separated and pursued in

different applications because of a "restriction requirement" issued by the PTO Examiners. (PFOF at ¶¶ 400-01, 440.) Thereafter, because the PTO calculated that it delayed the issuance of the initially examined '788 patent (but not the later '219 patent) by 1,079 days, it compensated for that delay by granting a PTA of that length to the '788 patent pursuant to 35 U.S.C. § 154. (*Id.* at ¶¶ 398-401.) As a result, while these two related patents have the same 20-year term based on their shared priority date, the '788 patent expires later based on its PTA. (*Id.* at ¶ 402.)

B. Zydus Will Not Establish That the '788 Patent's PTA Qualifies as an Improper Extension

Obviousness-type double patenting is a judicially created doctrine, derived from federal common law, intended to prevent an "improper timewise extension" of a patent's exclusivity by prohibiting claims in a second, later-expiring patent that are not patentably distinct.[35] *E.g.*, *In re Braat*, 937 F.2d 589, 592-95 (Fed. Cir. 1991). The '788 patent, however, was not improperly extended: the '788 patent expires later than the '219 patent only because of a statutorily authorized term extension resulting from government delay. (PFOF at Section X.A.)

Zydus nevertheless contends that the '219 patent is "a later-issued but earlier-expiring patent" that can invalidate the '788 patent (ZCF at 204) based on *Gilead Scis, Inc. v. Natco Pharma Ltd.*, 753 F.3d 1208 (Fed. Cir. 2014) (*see* Apr.

[35] Because Zydus's defense is legally flawed, there is no need to address the differences between the '788 and '219 patent claims. (PFOF at ¶ 496 n.108.)

13, 2018 Invalidity Contentions at 22-23). But that case did not involve an assertion of invalidity based on a PTA, and the Federal Circuit expressly stated in *Novartis AG v. Ezra Ventures LLC* that "[t]he effect of statutory term extensions was expressly ***not*** considered in *Gilead*."[36] 909 F.3d 1367, 1375 n.2 (Fed. Cir. 2018) (citing *Gilead*, 753 F.3d at 1215 n.6).

In *Novartis*, the Federal Circuit held that a statutory term extension based on FDA delay in approving a drug covered by the patent under 35 U.S.C. § 156, which is analogous to a PTA extending a patent term based on government delay in issuing the patent, is immune from obviousness-type double patenting challenges. 909 F.3d at 1372-73. In doing so, the court reasoned that the "judge-made double patenting doctrine" should not be used to "cut off a statutorily-authorized time extension," *id.* at 1375, which is consistent with longstanding Supreme Court precedent, *see, e.g.*, *SCA Hygiene Prod. Aktiebolag v. First Quality Baby Prod., LLC*, 137 S. Ct. 954, 960 (2017) (barring judge-made laches defense applying to a statute of limitations specified by Congress, and recognizing defense would give courts "a legislation-overriding role that is beyond the Judiciary's

[36] Instead, *Gilead* focused on preventing a "potential gamesmanship issue through structuring of priority claims." *Novartis*, 909 F.3d at 1374-75. Zydus does not, and cannot, assert that MTPC engaged in any such "tactics." *Id.*

power").[37] PTAs are likewise immune from such challenges, particularly given that, in 35 U.S.C. § 282(c), Congress equated PTAs and PTEs for purposes of defining how an "extension of a patent term or any portion thereof under section ***154(b) or 156***" can potentially be invalidated, which does not include obviousness-type double patenting. (PFOF at Section X.A.)

In short, Zydus has not provided any authority to permit such a judicial override of congressional authority in this situation, and its obviousness-type double patenting defense should be rejected for this reason alone.

C. The '788 Patent Claims Are Protected under the 35 U.S.C. § 121 Safe Harbor Provision

Even assuming, *arguendo*, that the '219 patent could be considered a double patenting reference, the '219 patent claims cannot invalidate claims 12 and 20 of the '788 patent based on the statutory safe harbor provided under 35 U.S.C. § 121. Pursuant to this provision, "a patent issuing . . . on an application filed as a result

[37] Invalidating such a statutory term extension with a judicially created doctrine would also be an improper taking in violation of the Takings and Due Process Clauses. *See, e.g.*, *Hartford-Empire Co. v. United States*, 323 U.S. 386, 415 (1945) ("That a patent is property, protected against appropriation both by individuals and by government, has long been settled."); *see also Stop the Beach Renourishment, Inc. v. Florida Dep't of Envtl. Protection*, 560 U.S. 702, 714-19 (2010) (plurality) ("If a legislature or a court declares that what was once an established right of private property no longer exists, it has taken that property, no less than if the State had physically appropriated it or destroyed its value by regulation."); *id*. at 735 (Kennedy, J., concurring in part) ("If a judicial decision . . . eliminates an established property right, the judgment could be set aside as a deprivation of property without due process of law.").

of [a restriction] requirement, shall not be used as a reference [against] the original application or any patent issued on" that application. As explained below, and as will be demonstrated at trial, this is precisely the case here and therefore creates an additional basis to reject Zydus's obviousness-type double patenting defense.

1. The '219 Patent Was Filed as a Result of the PTO's Restriction Requirement

"[W]hen the existence of multiple patents is due to the administrative requirements imposed by the [PTO], 35 U.S.C. § 121 provides that the inventor shall not be prejudiced by having complied with those requirements." *Applied Materials, Inc. v. Advanced Semiconductor Materials Am., Inc.*, 98 F.3d 1563, 1568 (Fed. Cir. 1996).[38] There is no dispute that, during the prosecution of the '788 patent, the PTO Examiners issued a "restriction requirement," which separated the 55 then-pending claims into 148 different invention groups so that the Examiners could focus on one group for searching and examination purposes. (PFOF at ¶ 440.) These invention groups fell into four general categories identified by the Examiners: (1) compounds; (2) methods of treatment using those compounds; (3) processes of making those compounds; and (4) combinations of those compounds and other drugs. (*Id.*)

[38] "The purpose of § 121 is to accommodate administrative convenience and to protect the patentee from technical flaws based on this unappealable examination practice." *Id.*; PFOF at Section X.C (summarizing relevant PTO procedures).

There is no dispute that, in response, MTPC elected Invention Group No. I, which was drawn to specific compound claims, including those found in original claim 10 (now claim 1 of the '788 patent). (*Id.* at Section X.E.1.b.) There is also no dispute that, after the restriction requirement was imposed, MTPC cancelled the method of treatment claims and subsequently pursued them in a "divisional" application that ultimately issued as the '219 patent.[39] (*Id.* at Sections X.E.1.b., X.E.2.) Accordingly, this application was filed "as a result" of the restriction requirement and cannot be used as a double patenting reference against the "original" application (*i.e.*, under 35 U.S.C. § 121). *See, e.g.*, *Boehringer Ingelheim Int'l GmbH v. Barr Labs., Inc.*, 592 F.3d 1340, 1353 n.3 (Fed. Cir. 2010) (noting that, absent the "administrative requirements imposed by the" PTO, the applicant could have maintained all of the claims in the original application).

Notwithstanding the above, Zydus contends that the Section 121 safe harbor does not apply because the restriction requirement was allegedly not "maintained with respect to the method of treatment claims." (ZCF at 222; Apr. 13, 2018 Invalidity Contentions at 24-25.) But the Examiners were explicit that they only ***partially*** withdrew the restriction requirement "with respect to" specific ***process of making*** "claims 38 and 39" (*i.e.*, the third general category above):

[39] Consistent with the safe harbor provisions of 35 U.S.C. § 121, the Examiner allowed these method of treatment claims without making any double patenting rejection over the '788 patent, which had issued by that time. (PFOF at ¶ 492.)

> The restriction requirement with respect to claims 38 and 39 was withdrawn in the office action dated June 2, 2009 and claims 38 and 39 were examined as set forth in the office action dated October 1, 2009. As was set forth in the office action dated June 2, 2009:

(PFOF at Section X.E.1.) Consistent with the PTO procedure cited by the Examiners ("MPEP § 821.04(B)"), they made clear that the restriction requirement otherwise remained in force, including with respect to the method of treatment claims. (*Id.* at ¶¶ 465-72.)[40]

Recognizing this, Zydus developed a new theory during expert discovery (*id.* at ¶ 406 n.95), namely that what Zydus characterizes as "voluntary acts" by MTPC should preclude application of the safe harbor. (ZCF at 222-27.) Zydus does not provide any law to support this position, which is in any event contradicted by the prosecution record. Specifically, MTPC made numerous attempts to "rejoin" the method of treatment claims, each of which the Examiners rejected, including after the compound claims elected for examination were allowed. (PFOF at Section X.E.1.b-e.) Only after these repeated rejections did MTPC cancel the method claims, but in doing so expressly "reserve[d] the right to pursue any cancelled subject matter in continuing applications" pursuant to the

[40] To the extent the Examiners were completely withdrawing the restriction requirement, they would not have relied upon MPEP § 821.04(b). (*Id.* at ¶ 470.)

Section 121 safe harbor. (*Id.* at ¶¶ 456, 461.) And MTPC did just that by filing a divisional application containing these method claims, which ultimately issued as the '219 patent. (*Id*. at Section X.E.2.) Accordingly, the '219 patent divisional application was "filed as a result" of the restriction requirement. 35 U.S.C. § 121.

2. Consonance Was Maintained Between the Claims of the '788 and '219 Patents

To qualify for Section 121 protection, "consonance" with the restriction requirement "as between" the two patents at issue must also be maintained. *E.g.*, *Boehringer*, 592 F.3d at 1354.[41] Zydus does not dispute that the '219 patent includes only method of treatment claims and that the '788 patent includes only compound claims, consistent with the Examiners' restriction requirement. (PFOF at ¶ 497.) As such, the consonance inquiry should end here.

Zydus alleges, however, that consonance was somehow violated *within* the original application that issued as the '788 patent because MTPC prosecuted original claim 10 as part of Invention Group No. I. (ZCF at 228; Apr. 13, 2018 Invalidity Contentions at 25.) The Federal Circuit has made clear, however, that an overlap of claims within a given application "is neither contrary to the restriction requirement nor relevant to the requirements of . . . § 121." *Boehringer*,

[41] "[C]onsonance requires . . . that the claims prosecuted in two or more applications having common lineage in a divisional chain honor, ***as between applications***, the lines of demarcation drawn by the examiner to what he or she considered independent and distinct inventions in the restriction requirement." *Id*.

592 F.3d at 1354. In other words, the goal of consonance is not to restrict claims *within* an application, but *as between* applications to ensure that the two sets of claims do not improperly overlap.[42]

Even if Zydus could present legal support for its argument, consonance would still not be violated because "the actual restriction groupings, not the written descriptions thereof, control for purposes of ascertaining" consonance. *Texas Instruments Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1179 (Fed. Cir. 1993). Here, the Examiners expressly included original claim 10 (*i.e.*, issued claim 1 of the '788 patent) in Invention Group No. I and no other group. (PFOF at ¶ 500.) Because the Examiners' restriction grouping—and not the written description thereof, which Zydus misconstrues (*id.* at ¶ 501)—controls, MTPC did not violate consonance by pursuing original claim 10 as part of Invention Group No. I, just as the Examiners expressly stated they should. (*Id.* at Section X.G.2.)

CONCLUSION

For the foregoing reasons, as well as the facts that will be proven at trial, the Court should find that Zydus has not met its burden of proving by clear and convincing evidence that the asserted claims are invalid. (PFOF at Section XI.)

[42] This is consistent with the fourth sentence of § 121, which provides that "[t]he validity of a patent shall not be questioned for failure of the [PTO] to require the application to be restricted to one invention." (PFOF at ¶¶ 542-43.)

Dated: May 28, 2020

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